PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
16866-38-1PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 27682	06/10/2000	07/10/1999
Applicant		
CIPHERGEN BIOSYSTEMS, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 6

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]US 00/27682

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, STRAND, EMBASE, MEDLINE, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 37811 A (AN GANG ;UROCOR INC (US); VELTRI ROBERT W (US)) 29 July 1999 (1999-07-29)	1,2, 5-11,13, 14, 17-21, 50,51, 53,55, 57-60, 79-83
Y	abstract claims 1,2,8,28,32	1,10,11, 13,22,23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 April 2001	12/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gundlach, B

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]US 00/27682

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	MALM JOHAN ET AL: "Isolation and characterization of the major gel proteins in human semen, semenogelin I and semenogelin II." EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 238, no. 1, 1996, pages 48-53, XP000997222 ISSN: 0014-2956 page 49, right-hand column, paragraph 4 ---	1,10,11, 13,22,23
A	WO 98 40738 A (SLOAN KETTERING INST CANCER ;BLOBEL CARL (US); ROTHMAN JAMES (US);) 17 September 1998 (1998-09-17) page 15, line 29 -page 16, line 2 ---	1,10,11, 13,22,23
X	DUBE JEAN Y: "Can prostatic kallikrein kH2 favor prostatic cancer progression?" M-S (MEDECINE SCIENCES), vol. 14, no. 1, January 1998 (1998-01), pages 111-113, XP000997204 ISSN: 0767-0974 abstract; figure 1 page 112, left-hand column, paragraph 2 ---	1,4
A	DENMEADE S R ET AL: "SPECIFIC AND EFFICIENT PEPTIDE SUBSTRATES FOR ASSAYING THE PROTEOLYTIC ACTIVITY OF PROSTATE-SPECIFIC ANTIGEN" CANCER RESEARCH,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD,US, vol. 57, 1 November 1997 (1997-11-01), pages 4924-4930, XP002070515 ISSN: 0008-5472 page 4929, left-hand column, paragraph 4 -right-hand column ---	1-83
A	WO 96 00503 A (DEFEO JONES DEBORAH ;FENG DONG MEI (US); OLIFF ALLEN I (US); GARSK) 11 January 1996 (1996-01-11) page 1 -page 2, line 9; example 1 ---	1-83
A	WO 97 12624 A (DEFEO JONES DEBORAH ;FENG DONG MEI (US); OLIFF ALLEN I (US); GARSK) 10 April 1997 (1997-04-10) abstract; example 1 ---	1-83
P,X	WO 99 61471 A (INCYTE PHARMA INC ;PATTERSON CHANDRA (US); CORLEY NEIL C (US); YUE) 2 December 1999 (1999-12-02) page 49, line 29 -page 51, line 14 page 52, line 3 -----	1-4, 13-17

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
US 00/27682

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9937811	A	29-07-1999	US	5873328 A	23-02-1999
			US	5972615 A	26-10-1999
			EP	1047793 A	02-11-2000
			AU	2327099 A	09-08-1999
			US	6171796 B	09-01-2001
WO 9840738	A	17-09-1998	EP	0975963 A	02-02-2000
WO 9600503	A	11-01-1996	US	5599686 A	04-02-1997
			AU	689934 B	09-04-1998
			AU	3092295 A	25-01-1996
			BG	101077 A	27-02-1998
			BR	9508151 A	30-03-1999
			CA	2192957 A	11-01-1996
			CN	1156964 A	13-08-1997
			CZ	9603810 A	16-04-1997
			EP	0771209 A	07-05-1997
			FI	965225 A	26-02-1997
			HU	76350 A	28-08-1997
			JP	10502619 T	10-03-1998
			NO	965592 A	28-02-1997
			NZ	290239 A	25-11-1998
			PL	317872 A	28-04-1997
			RO	116198 B	30-11-2000
			SK	164096 A	04-06-1997
			US	6143864 A	07-11-2000
			US	5866679 A	02-02-1999
WO 9712624	A	10-04-1997	US	5866679 A	02-02-1999
			AU	7203496 A	28-04-1997
			CA	2233272 A	10-04-1997
			EP	0853483 A	22-07-1998
			JP	10512588 T	02-12-1998
			US	6130204 A	10-10-2000
WO 9961471	A	02-12-1999	AU	4409099 A	13-12-1999
			EP	1080194 A	07-03-2001

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 July 2001 (17.07.01)	
International application No. PCT/US00/27682	**Applicant's or agent's file reference** 16866-38-1PC
International filing date (day/month/year) 06 October 2000 (06.10.00)	**Priority date** (day/month/year) 07 October 1999 (07.10.99)
Applicant YIP, Tai-Tung et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 April 2001 (18.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer H. Zhou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PKS

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PARENT, Annette S.
Townsend and Townsend and Crew LLP
Two Embarcadero Center
8th Floor
San Francisco, CA 94111-3834
ETATS-UNIS D'AMERIQUE

PTO/PCT Rec'd 25 MAR 2002

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	06.08.2001
Applicant's or agent's file reference: 16866-38-1PC	**REPLY DUE** 11/6/01 **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/27682	06/10/2000	07/10/1999

International Patent Classification (IPC) or both national classification and IPC

G01N33/574

Applicant

CIPHERGEN BIOSYSTEMS, INC. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07/02/2002.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Moreno de Vega, C

Formalities officer (incl. extension of time limits)

Danti, B

Telephone No. +49 89 2399 8161

Form PCT/IPEA/408 (cover sheet) (January 1994)

Response 11/6/01

DOCKETED

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-4,6-35	as originally filed				
5,5a	as received on	30/04/2001	with letter of	30/04/2001	

Claims, No.:

1-83	as originally filed

Drawings, sheets:

1/6-6/6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims
Inventive step (IS)	Claims
Industrial applicability (IA)	Claims

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99 37811 A (AN GANG; UROCOR INC (US); VELTRI ROBERT W (US)) 29 July 1999 (1999-07-29)

D2: MALM JOHAN ET AL: 'Isolation and characterization of the major gel proteins in human semen, semenogelin I and semenogelin II.' EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 238, no. 1, 1996, pages 48-53, XP000997222 ISSN: 0014-2956

1. Novelty - Article 54 EPC

D1 (see claims 1, 2, 8, 28 and 32 and page 51 line 6 - page 6 line 16) discloses methods of diagnosing a metastasic prostate disease state detecting a difference in quantitiy of expression of metastasic prostate disease marker gene, e.g. semenogelin II, using an antibody immunoreactive with semenogelin II and detecting the immunocomplex by ELISA, and a kit therefor.
D2 discloses the determination of purified SgI (Ma 49 958 Da) and SgII (Ma 63 539) by matrix-assisted laser desorption mass spectrometry.

The subject-matter of present claims 1-83 appears to be novel, because the known prior art discloses neither the methods for diagnosing prostate cancer determining polypeptide markers of Ma < 27.000 which is differentially present in samples of a prostate cancer patient and a benign prostate hyperplasia patient, nor the kits therefor as in claims 61-83.

2. Inventive step - Article 56 EPC

D1, which is considered to be the prior art with respect of the present invention, differs from it in that a) higher Ma proteins are determined and that no reference is done to polypeptides resulting from the PSA-mediated cleavage with different expression in PC (prostate cancer) and BPH (benign prostate hyperplasia), b) fails to disclose the kits of the present invention, which comprise absorbent substrates containing a metal chelating group and suitable for measuring by gas phase ion spectrometry. The technical problem to be solved by the present invention is the provision of quick and accurate methods and kits for determining if a patient has prostate cancer. The solution provided by claims 1-83 is based on monitoring markers that are cleaved products generated by PSA-mediated proteolysis, and that are differentially present in samples of a PC patient and a BPH patient. The usefulness of said polypeptides to differentiate said conditions has not been suggested in the prior art. Therefore, claims 1-83 are considered to be inventive.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99/61471	2/12/99	28/5/1999	29/5/1998

The priority of the present application is assumed to be valid. Should the present application be entered into the regional phase, the above document would not be relevant to the question of novelty. It discloses human transmembrane proteins (HTMPN) and methods for diagnosing disorders associated with their expression. Among others conditions prostate cancer is mentioned (page 52 line 3), but no specific reference of the localization of said protein is to be found in that document.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

1. It is clear from the description on page 15 that the following feature is essential to the definition of the invention: by the methods and kits of the invention, markers that are cleaved products generated by PSA-mediated proteolysis are monitored, in order to provide a more sensitive way to determine whether a patient has BPH or prostate cancer.

   Since independent claims 1, 24 and 50 do not contain this feature, they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

2. The relative terms "differentially present" used in claims 1, 13, 24, 50, 61 and 79 have no well-recognised meaning and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

3. The wording "seminal basic protein" used in the claims is unclear (Article 6 PCT). It should be explained at least in claim 3, where it is first mentioned.

PATENT COOPERATION TREATY

PKS

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PARENT, Annette S.
Townsend and Townsend and Crew LLP
Two Embarcadero Center
8th Floor
San Francisco, CA 94111-3834
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	04.12.2001
Applicant's or agent's file reference: 16866-38-1PC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/27682	06/10/2000	07/10/1999

Applicant: CIPHERGEN BIOSYSTEMS, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

4/762

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Danti, B Tel.+49 89 2399-8161

Form PCT/IPEA/416 (July 1992)

Km

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
16866-38-1PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/27682	06/10/2000	07/10/1999
International Patent Classification (IPC) or national classification and IPC G01N33/574		
Applicant CIPHERGEN BIOSYSTEMS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/04/2001	04.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Moreno de Vega, C Telephone No. +49 89 2399 7486

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/27682

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-4,6-35	as originally filed				
5,5a	as received on	30/04/2001	with letter of	30/04/2001	

Claims, No.:

1-83	as originally filed

Drawings, sheets:

1/6-6/6	as originally filed

Sequence listing part of the description, pages:

fig. 1, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☒ furnished subsequently to this Authority in written form.
   ☒ furnished subsequently to this Authority in computer readable form.
   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☒ The statement that the information recorded in computer readable form is identical to the written sequence

listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-83
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-83
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-83
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99 37811 A (AN GANG; UROCOR INC (US); VELTRI ROBERT W (US)) 29 July 1999 (1999-07-29)

D2: MALM JOHAN ET AL: 'Isolation and characterization of the major gel proteins in human semen, semenogelin I and semenogelin II.' EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 238, no. 1, 1996, pages 48-53, ISSN: 0014-2956

1. Novelty - Article 54 EPC

D1 (see claims 1, 2, 8, 28 and 32 and page 51 line 6 - page 6 line 16) discloses methods of diagnosing a metastasic prostate disease state detecting a difference in quantitiy of expression of metastasic prostate disease marker gene, e.g. semenogelin II, using an antibody immunoreactive with semenogelin II and detecting the immunocomplex by ELISA, and a kit therefor.
D2 discloses the determination of purified SgI (Ma 49 958 Da) and SgII (Ma 63 539) by matrix-assisted laser desorption mass spectrometry.

The subject-matter of present claims 1-83 appears to be novel, because the known prior art discloses neither the methods for diagnosing prostate cancer determining polypeptide markers of Ma < 27.000 which is differentially present in samples of a prostate cancer patient and a benign prostate hyperplasia patient, nor the kits therefor as in claims 61-83.

2. Inventive step - Article 56 EPC

D1, which is considered to be the prior art with respect of the present invention, differs from it in that a) higher Ma proteins are determined and that no reference is done to polypeptides resulting from the PSA-mediated cleavage with different expression in PC (prostate cancer) and BPH (benign prostate hyperplasia), b) fails to disclose the kits of the present invention, which comprise absorbent substrates containing a metal chelating group and suitable for measuring by gas phase ion spectrometry. The technical problem to be solved by the present invention is the provision of quick and accurate methods and kits for determining if a patient has prostate cancer. The solution provided by claims 1-83 is based on monitoring markers that are cleaved products generated by PSA-mediated proteolysis, and that are differentially present in samples of a PC patient and a BPH patient. The usefulness of said polypeptides to differentiate said conditions has not been suggested in the prior art. Therefore, claims 1-83 are considered to be inventive.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99/61471	2/12/99	28/5/1999	29/5/1998

The priority of the present application is considered to be valid. Should the present application be entered into the regional phase, the above document would not be relevant to the question of novelty. It discloses human transmembrane proteins (HTMPN) and methods for diagnosing disorders associated with their expression. Among others conditions prostate cancer is mentioned (page 52 line 3), but no specific reference of the localization of said protein is to be found in that document.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

1. It is clear from the description on page 15 that the following feature is essential to the definition of the invention: by the methods and kits of the invention, markers that are cleaved products generated by PSA-mediated proteolysis are monitored, in order to provide a more sensitive way to determine whether a patient has BPH or prostate cancer.

   Since independent claims 1, 24 and 50 do not contain this feature, they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

2. The relative terms "differentially present" used in claims 1, 13, 24, 50, 61 and 79 have no well-recognised meaning and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

3. The wording "seminal basic protein" used in the claims is unclear (Article 6 PCT). It should have been explained at least in claim 3, where it is first mentioned.

4. Instructions for using a kit represent presentation of information in the sense of Rule 67.1(v) PCT. The said feature is therefore not of technical character. It is, in this instance, noted that a skilled person is not bound to added written instructions, but will use the immunoassay components according to the

common knowledge.

If one tries to derive a technical sense from the presence of added instructions, this would strictly concern the use or application of the kit. The intended use does in the present case not confer any definition of limitation of the product as such.

Consequently, the feature has either to be ignored in the assessment of novelty and inventive step of the claims or, if not being ignored, its presence raises uncertainty as to the scope and category of the claim, contrary to Art. 6 PCT.

In one embodiment, the substrate in the kit is in the form of a probe which is removably insertable into a gas phase ion spectrometer. In another embodiment, the kit further comprises another substrate which can be used together with the substrate comprising the adsorbent to form a probe which is removably insertable into a gas phase ion spectrometer.

In another embodiment, the kit further comprises instructions for suitable operational parameters.

In yet another embodiment, the substrate comprises a hydrophobic group and an anionic group as an adsorbent. In yet another embodiment, the substrate comprises a hydrophobic group as an adsorbent. In yet another embodiment, the substrate comprises a metal chelating group. In yet another embodiment, the substrate comprises a metal chelating group complexed with a metal ion as an adsorbent. In yet another embodiment, the substrate comprises an antibody that specifically binds to a marker, preferably seminal basic protein, as an adsorbent. In yet another embodiment, the washing solution is an aqueous solution.

In yet another embodiment, the kit comprises an antibody that specifically binds to the marker, and a detection reagent. Optionally, the antibody can be immobilized on a solid support.

In yet another embodiment, the kits can further comprise a standard indicating a diagnostic amount of the marker.

While the absolute identity of many markers is not yet known, such knowledge is not necessary to measure them in a patient sample, because they are sufficiently characterized by, *e.g.*, mass and by affinity characteristics. It is noted that molecular weight and binding properties are characteristic properties of these markers and not limitations on means of detection or isolation. Furthermore, using the methods described herein or other methods known in the art, the absolute identity of the markers can be determined.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the amino acid sequence of seminal basic protein (SEQ ID NO:1).

Figure 2 illustrates a probe comprising spots of adsorbents on the probe surface.

PATENT

Attorney Docket No.: 16866-38-1PC

EUROPEAN PATENT OFFICE

In re application of:

Ciphergen Biosystems, Inc. *and*
Eastern Virginia Medical School

Application No.: PCT/US00/27682

Filed: October 6, 2000

For: PROSTATE CANCER MARKER PROTEINS

LETTER REGARDING AMENDMENT PURSUANT TO ARTICLE 34(2)(b)

European Patent Office
Erhardstrasse 27
D-80298 Munich 2
Germany

Sir:

Applicant respectfully requests that the IPEA amend the application by replacing page 5 with the enclosed replacement pages 5 and 5A.

Replacement pages 5 and 5A have been amended to show Sequence ID Number 1.

The Demand for International Preliminary Examination was filed on 18 April 2001.

Respectfully submitted,

Peter Seperack

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